The Mental Health Consequences of Torture

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Neurobiological Models of Posttraumatic Stress Disorder

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Posttraumatic stress disorder (PTSD) is commonly understood as a psychological disorder that results from exposure to life-threatening situations. Symptoms of reexperiencing, avoidance, and increased arousal are frequently treated with psychologically based interventions, including individual and group psychotherapy, behavior therapy, and psychoeducation. In recent years, however, it has become increasingly clear that PTSD also can be understood from a biological perspective.

Multiple neurobiological systems become activated when an organism is threatened. Parallel activation of various brain regions and neurotransmitter systems allows the organism to assess and appropriately respond to potential dangers. This highly complex process contributes to the development of anxiety, fear, and the fight–flight response that allows the organism to protect itself by either fleeing from or actively confronting danger. Whereas this process generally serves a protective role in the short run, it appears that maladaptive responses to stress can ensue in individuals who develop PTSD (Charney, Deutch, & Krystal, 1993).

In this chapter, we will focus on two neurobiological systems that are critical for survival—the sympathetic nervous system and the hypothalamic–pituitary–adrenal axis (HPA). To date, most neurobiological research in PTSD has focused on these two systems. It is clear that numerous other neurobiological systems, such as the opiate, serotonin, and dopamine systems, also are involved in acute and chronic responses to stress, although far less is known about them as they relate to PTSD.

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How these stress-related neurobiological systems interact with one another in complex ways is only partially understood (Southwick, Krystal, Johnson, & Charney, 1992).

This chapter will also describe several neurobiological models of PTSD. These models grow out of animal and human studies and represent an attempt to understand the rapidly growing body of trauma-related neurobiological research.

SYMPATHETIC NERVOUS SYSTEM ALTERATIONS IN PTSD

The sympathetic nervous system plays a central role in the organism's fight–flight response by increasing blood flow to muscles and vital organs, dilating pupils, limiting blood loss, and mobilizing energy for use by large muscle groups. Epinephrine (adrenaline) and norepinephrine (noradrenaline), both catecholamines, are two key neurotransmitters that facilitate the above sympathetic nervous system functions (Cannon, 1914; Gagnon, 1977; Mountcastle, 1973). They also play an important role in the development of fear and in the organism's ability to selectively focus on, respond to, and then remember the feared stimulus (Aston-Jones, Valentino, & Van Bockstaele, 1994; Gold & McCarty, 1995; Liang, Juler, & McGaugh, 1990; McGaugh, 1989; Zigmond, Finlay, & Sved, 1995).

Since World War II, numerous psychophysiological studies have documented the heightened sympathetic nervous system arousal of combat veterans who suffer from PTSD (Orr, 1990; Prins, Kaloupek, & Keane, 1995). Psychophysiological studies typically measure biological parameters such as heart rate, blood pressure, and skin conductance and electromyographic activity of facial muscles at baseline and in response to various trauma-relevant stimuli and neutral stimuli and generic stressors. Trauma-relevant stimuli include auditory and visual reminders of traumas similar to the one experienced by the participant as well as script-driven imagery of the individual's own specific traumatic experience.

A review of this extensive literature shows that trauma victims with PTSD demonstrate greater psychophysiological reactivity (especially heart rate) to trauma-relevant stimuli than do comparison groups such as trauma victims without PTSD and nontraumatized healthy controls. Although some studies have reported a higher baseline resting heart rate in PTSD compared with control groups, most studies have found no differences (Orr, 1990; Prins et al., 1995). Further, response to generic stressors typically has been the same between PTSD and non-PTSD groups (McFall, Murburg, & Ko, 1990; Pitman et al., 1990). In summary, trauma victims with PTSD appear to have normal resting sympathetic nervous system activity (as reflected by heart rate and blood pressure) that becomes abnormally reactive in response to specific reminders of a personally experienced trauma but not in response to generic stressors (Murburg, 1994; Prins et al., 1995).

Biochemical correlates of this heightened sympathetic nervous system activity in veterans and civilians with PTSD include increased excretion of epinephrine and norepinephrine in urine collected over a 24-hour period (L. M. Davidson & Baum, 1986; DeBellis, Baum, Birmaher, & Ryan, 1997; Kosten, Mason, & Giller, 1987; Yehuda, Southwick, & Giller, 1992) and decreased numbers of alpha-2 adrenergic receptors on the surface of platelets (circulating blood elements) (Perry, 1994; Perry, Giller, & Southwick, 1987). For epinephrine and norepinephrine to have a physiological effect, they must first attach to adrenergic receptors. A decrease in the number of adrenergic receptors most likely results from chronic elevation of circulating epinephrine and norepinephrine. Thus, as a group, individuals with PTSD appear to have higher levels of epinephrine and norepinephrine than nontraumatized individuals even many years after a trauma.

This increase in epinephrine and norepinephrine may not be present during calm, resting states. However, it appears that PTSD subjects, as a group, respond to a variety of stressors with exaggerated increases in catecholamines compared with healthy controls (McFall et al., 1990; Murburg, 1994; Southwick, Bremner, Krystal, & Charney, 1994; Southwick et al., 1993; Southwick, Yehuda, & Morgan, 1995). For example, greater increases in epinephrine have been observed in veterans with war-related PTSD compared with controls during and after viewing a combat film but not in response to a film depicting an automobile accident (McFall et al., 1990). Exaggerated increases in catecholamines also have been noted in response to pharmacological provocation. To more directly assess adrenergic responsivity of both the peripheral and central nervous system, one study administered intravenous yohimbine to 20 Vietnam combat veterans with PTSD and 18 healthy controls (Southwick et al., 1993). Yohimbine is an alpha-2 adrenergic receptor antagonist that activates noradrenergic neurons by blocking the alpha-2-adrenergic autoreceptor, thereby increasing the release of endogenous norepinephrine. Yohimbine caused panic attacks in 70% and flashbacks in 40% of combat veterans with PTSD but had minimal effects in the control group. Subjects with PTSD also had significantly greater increases in heart rate and a greater than twofold increase in methoxyhydroxyphenylglycol (MHPG), a breakdown product of norepinephrine.

In a recent positron emission tomography (PET) study (Bremner, Innis, et al., 1997), the effect of yohimbine on the brain activity of 10 combat veterans with PTSD was compared with that of 10 healthy controls. A single bolus of [F-18]2-fluoro-2-deoxyglucose was administered to each subject following either yohimbine or placebo infusion. Subjects were then scanned, and PET images were reconstructed to determine brain-tissue activity. Yohimbine caused an exaggerated release of plasma MHPG and a relative decrease in brain metabolism. It was hypothesized that this relative decrease in brain metabolism may have resulted in a possible increase in signal-to-noise ratio and vigilance among combat veterans with PTSD as compared with normal controls. Taken together, the above catecholamine findings suggest that at least a subgroup of individuals with PTSD has increased responsivity of the sympathetic nervous system that is most evident when the individual is restressed (Murburg, 1994; Southwick et al., 1995).

THE HYPOTHALAMIC–PITUITARY–ADRENAL AXIS

Whereas the sympathetic nervous system prepares the organism to react to stressful stimuli, the HPA axis appears to serve a catabolic restorative role (Munck, Guyre, & Holbrook, 1984; Yehuda, 1997). When an organism is stressed, the hypothalamus releases corticotropin-releasing hormone (CRH), which then stimulates the release of adrenocorticotropic hormone (ACTH) from the pituitary gland. ACTH in turn stimulates the adrenal gland to release cortisol, which helps to terminate a variety of neurobiological reactions that have been set in motion by stressful stimuli.

Under normal circumstances, cortisol rises in response to stress. However, several recent studies have found that trauma victims who develop PTSD have lower initial cortisol responses to a traumatic event than trauma victims who do not develop PTSD (McFarlane, Atchison, & Yehuda, 1997; Resnick, Yehuda, & Acierno, 1997). Further, in studies of civilians and veterans with chronic PTSD, baseline plasma cortisol levels and 24-hour urine cortisol excretion have been reported as low compared with controls (Yehuda, Giller, Levengood, Southwick, & Siever, 1995). In combat veterans with chronic PTSD, these low plasma levels of cortisol have been reported throughout the day and night, especially in the very early morning and late evening (Yehuda, 1997).

Receptor-binding studies, however, have found an increased number of glucocorticoid receptors in subjects with PTSD compared with nontraumatized controls (Yehuda, 1997; Yehuda, Giller, et al., 1995). An increased number of receptors would enhance sensitivity by providing more binding sites for cortisol. Consistent with increased receptor number and sensitivity is the finding that subjects with PTSD hyperrespond to administration of dexamethasone, a synthetic glucocorticoid that acts like cortisol (Yehuda, 1997; Yehuda, Boisoneau, & Lowy, 1995; Yehuda, Giller, et al., 1995; Yehuda, Southwick, & Krystal, 1993). Normally, when dexamethasone is administered to healthy individuals, it stimulates glucocorticoid receptors that serve as part of a negative feedback mechanism. When stimulated, these receptors signal the hypothalamus and pituitary to decrease the release of CRH and ACTH, which in turn results in decreased stimulation of the adrenal gland and diminished release of endogenous cortisol. In several different populations of trauma survivors with PTSD, dexamethasone has an exaggerated effect with the result that endogenous cortisol release is reduced to a greater degree than in normal controls. This finding is consistent with an increased number of glucocorticoid receptors and increased negative feedback at the level of the hypothalamus and pituitary in traumatized individuals with PTSD compared with controls (Yehuda, Giller, et al., 1995). These findings in PTSD differ markedly from findings in studies of major depressive disorder (American Psychiatric Association Task Force on Laboratory Tests in Psychiatry, 1987).

Other important HPA axis findings in combat veterans with PTSD include elevated CRH levels in the cerebrospinal fluid (Bremner, Licinio et al., 1997), blunted ACTH response to CRH infusion (Smith, Davidson, & Ritchie, 1989), and increased ACTH response to metyrapone (Yehuda, 1997). In conjunction with plasma and 24-hour urine cortisol, glucocorticoid receptor, and dexamethasone suppression studies, these findings are consistent with the notion of enhanced negative feedback of the HPA axis and elevated CRH release in PTSD (Yehuda, 1997). It has been hypothesized that these alterations help to explain why individuals with PTSD hyperrespond to stress (Yehuda, 1997).

STRESS SENSITIZATION

Sensitization refers to a stressor-induced increase in behavioral or physiological responsiveness following exposure to subsequent stressors of the same or lesser magnitude (Post, 1992; Post, Weiss, & Smith, 1995; Sorg & Kalivas, 1995). When a neurobiological system becomes sensitized, its behavioral, physiological, and biochemical responses to a given stressor gradually increase. The time interval between the initial stressors appears to be an important factor in the development of sensitization. If sufficient time has passed between the initial stressor and subsequent stressors, a single stressful stimulus may be capable of initiating behavior sensitization. The capacity to respond more readily to future stressors may be adaptive with regard to survival (Post et al., 1995; Sorg & Kalivas, 1995). The organism is better prepared for future dangers. However, it appears that sensitization may also be maladaptive, leaving the organism in a hyperreactive state in which it overresponds to minor stressors. The organism may become hypervigilant and continue to act biologically as if a danger exists even when no real danger is currently present (Southwick et al., 1995).

Neurochemical and neuroanatomical systems mediating sensitization are only partially understood. Most extensively studied in the development and maintenance of stress-induced sensitization in mammals have been catecholamine systems (especially dopamine and norepinephrine). For example, limited shock exposure that does not increase norepinephrine utilization in control rats does increase norepinephrine release in animals previously exposed to the stressor (Anisman & Sklar, 1978; Irwin, Ahluwalia, & Anismar, 1986). Similarly, equivalent doses of yohimbine have been shown to cause significantly greater increases in anxiety, vigilance, intrusive traumatic memories, heart rate, and plasma MHPG in combat veterans with PTSD compared with healthy controls (Southwick et al., 1993). This finding is consistent with a behavioral sensitization model of PTSD.

A large body of evidence also suggests that the HPA axis can become sensitized in trauma victims with PTSD. Consistent with a sensitization model (Yehuda, 1997), most HPA axis studies in veterans and civilians with PTSD have found decreased plasma cortisol and decreased 24-hour urine cortisol, but larger numbers of plasma lymphocyte glucocorticoid receptors and increased suppression of cortisol by the synthetic glucocorticoid dexamethasone. A larger number of glucocorticoid receptors at the level of the hypothalamus and the pituitary may explain why cortisol and dexamethasone appear to have an exaggerated inhibitory effect on HPA axis function.

Although sensitization has not been shown clearly in clinical studies of traumatized subjects, it has been hypothesized that sensitization of sympathetic nervous system and HPA axis function may contribute to a number of PTSD symptoms including hypervigilance, irritability, poor concentration, insomnia, exaggerated startle, and, perhaps, intrusive memories (Charney et al., 1993; Yehuda, 1997). Whereas most neurobiological studies in traumatized humans have focused on the sympathetic nervous system and the HPA axis, preliminary evidence exists that other neurobiological systems, including the serotonin system (Arora, Fitcner, & O'Connor, 1993; Southwick et al., 1997), also may be sensitized in trauma survivors with PTSD. Exactly how various neurobiological stress systems interact during the acute and chronic phases of trauma and thereafter are not well understood. However, it is possible that sensitization (increased negative feedback) of the HPA axis results in decreased levels of cortisol and thus a diminished capacity to terminate the sympathetic nervous system's response to traumatic stress (Yehuda, 1997). Overall, a behavioral sensitization model appears to fit many of the findings reported to date in subjects with PTSD in which systems gradually become hyperresponsive to stress. Further, recent evidence suggests that sensitization may be associated with changes in gene expression (Post et al., 1995).

FEAR CONDITIONING

Numerous researchers have noted a remarkable similarity between the effects of fear conditioning in animals and the behavioral and physiological responses seen in combat veterans with severe war neuroses (Kardiner & Spiegel, 1947; Keane, Fairbank, & Caddell, 1985; Kolb, 1987). Fear conditioning involves the pairing of a fear-provoking aversive event (unconditioned stimulus, or US) with an explicit neutral stimulus (conditioned stimulus, or CS) that then serves as a specific reminder of the trauma or aversive event. For example, if a neutral light is paired with an aversive stimulus such as a shock, eventually the light by itself (in the absence of the shock) can elicit fear and fear-related physiologic responses. The light becomes an explicit conditioned stimulus (Grillon, Southwick, & Charney, 1996). Conditioning also can occur to contextual cues that were present during the pairing of the CS and US (Bolles & Fanselow, 1980; Foa, Zinbarg, & Rothbaum, 1992). Thus, the cage in which the shock was delivered can become a contextual cue with the capacity to evoke fear in the absence of either aversive unconditioned stimuli (e.g., shock) or explicit conditioned stimuli (e.g., light).

As an example, after surviving a life-threatening fire (US) in which others were killed, a combat veteran may no longer experience the smell of burning wood as a neutral stimulus that evokes feelings of peace and comfort. Instead, the smell now may serve as an explicit CS that is capable of evoking fear and fear-related behaviors. Other contextual stimuli that were present at the time of the fire, but that were not directly associated with the fire, also can acquire the capacity to evoke fear. Thus, if the fire occurred on a hot and muggy day, many years later hot and muggy days, even in locations thousands of miles away from the original fire, may leave the veteran feeling anxious and irritable (Southwick et al., 1994).

The neurobiological underpinnings of fear conditioning are not completely understood. However, it is clear that the amygdala plays a pivotal role in both unconditioned and conditioned fear (Aggleton, 1992; Blanchard & Blanchard, 1972). The amygdala is a structure in the limbic system that receives rich input from sensory regions of the cortex and from numerous subcortical regions. It also has extensive efferent, or outgoing, neuronal connections to autonomic, motor, and neuroendocrine systems. This rich array of neuronal input and output makes the amygdala ideally suited for its role in assessing and responding to emotionally significant stimuli such as those that indicate potential threat (Aggleton, 1992).

In animals, electric stimulation of the amygdala produces fear-related behaviors, whereas lesions of the amygdala have been shown to reduce fear and aggression as well as the overall ability to attach meaning to sensory information, a capacity that allows the organism to generate appropriate behavioral responses. In general, amygdala neuronal activity is increased with stimuli of high emotional significance, especially threat. It also has been demonstrated that a formerly neutral stimulus that has been conditioned to a fear-related stimulus (US) can, on its own, increase neuronal firing in the amygdala and that lesions of the amygdala attenuate fear-related behaviors seen in response to fear-conditioned stimuli (CS). Thus, the amygdala is highly responsive to both unconditioned and conditioned fear cues (Charney, Deutch, Southwick, & Krystal, 1995).

Separate neurobiological mechanisms appear to mediate explicit fear conditioning and contextual fear conditioning. Although much evidence suggests that the amygdala is involved in both types of conditioning (Aggleton, 1992; Blanchard & Blanchard, 1972; Davis, 1992), the hippocampus appears to play a critical role in contextual but not explicit fear conditioning (Phillips & LeDoux, 1992). The hippocampus is a limbic structure that plays a key role in processing spatial and contextual cues with an emphasis on the relationship of multiple stimuli (O'Keefe, 1993; O'Keefe & Nadel, 1978; Parkinson, Murray, & Mishkin, 1990). Lesions of the hippocampus attenuate fear responses to conditioned contextual stimuli but not conditioned explicit stimuli (O'Keefe & Nadel, 1978; Phillips & LeDoux, 1992). Thus, after hippocampal lesions, animals are no longer afraid of the cage (contextual stimuli) in which shock was delivered but are still afraid of the explicit stimulus (light) that was paired with the shock. Research evidence also suggests that various neurotransmitters, such as noradrenaline and acetylcholine, have differential roles in explicit and contextual conditioning (McAlonan, Wilkinson, Robbins, & Everitt, 1995; Selden, Everitt, Jarrard, & Robbins, 1991).

Fear conditioning can occur very rapidly (Blanchard, Yudko, Rodgers, & Blanchard, 1993; LeDoux, 1996). For example, in some cases, a neutral stimulus can become conditioned to fear after a single pairing with an unconditioned fear stimulus. This pairing allows the organism to avoid lengthy trial-and-error learning about situations that are potentially dangerous. Rapid conditioning of characteristics of the danger itself (explicit stimuli) and characteristics of the place in which the danger occurred (contextual stimuli) maximize future chances for survival (LeDoux, 1996).

Fear conditioning also can occur outside of conscious awareness (LeDoux, 1996; Ohman, 1992). Thus, the traumatized human may not be consciously aware that a formerly neutral stimulus has become frightening through its association with an unconditioned fear stimulus. This concept applies for both explicit and contextual stimuli. The result may be an individual who becomes anxious, irritable, or frightened for reasons that he or she does not understand. The earlier cited trauma victim, for example, may become anxious or frightened on hot, muggy days without having any conscious appreciation for the cause of these feelings.

Once established, fear conditioning can last for long periods of time. Theoretically, once a conditioned fear stimulus is no longer associated with an aversive outcome, the conditioned fear response should extinguish. However, recent evidence suggests that extinction is an active process that involves new learning. The old fear-conditioned learning has not really been extinguished or replaced (LeDoux, Farb, & Ruggiero, 1990). This finding has led to the suggestion that subcortical fear-related learning is essentially indelible in nature (Bouton, 1994; LeDoux, 1996). Even though the fear-conditioned response seems to have disappeared over time, it can return under the right circumstances.

ENHANCED MEMORY FOR AVERSIVE EVENTS

A large body of evidence suggests that arousing, fearful, or emotionally exciting events are remembered better and for longer periods of time than emotionally neutral events (McGaugh, 1989). Such arousing events reportedly can produce what Brown and Kulik (1977) have termed flashbulb memories that resemble a photographic print. It has been proposed that emotional arousal activates neurobiological systems that facilitate the encoding and consolidation of memory. Enhanced memory for arousing situations may have significance for survival. The organism that remembers arousing and dangerous situations may be less vulnerable to similar potentially dangerous situations in the future. Unfortunately, these memories (in the form of intrusive recollections and nightmares) also may repetitively haunt the trauma survivor long after the event (LeDoux, 1996; Reiser, 1991).

Animal and human studies strongly suggest that enhanced memory for emotionally arousing, stressful, and traumatic events may, in part, be mediated by catecholamines (adrenaline, noradrenaline). Gold and Van Buskirk (1975) reported that posttraining injections of epinephrine enhanced retention for an inhibitory avoidance task in rats with intact adrenal glands. Enhanced retention was dependent on both dose and time. Norepinephrine, particularly in the amygdala, is also involved in learning and memory. Intra-amygdala infusion of norepinephrine immediately after training for a variety of learning tasks enhanced retention (Liang et al., 1990).

It has been hypothesized that highly stressful traumatic events can cause overstimulation of endogenous stress-responsive neuromodulators such as epinephrine and norepinephrine and that these neuromodulators cause an overconsolidation of memory for the event. The resulting, deeply engraved traumatic memory would then be responsible for conditioned emotional responses and intrusive recollections typically seen in PTSD (Pitman, 1989). Further, when the traumatic event is relived through intrusive recollections, flashbacks, and nightmares, epinephrine and norepinephrine are again released, leading to an additional strengthening of the memory trace and an even greater likelihood of subsequent intrusive recollections. This positive-feedback loop could explain the progression from subclinical to clinical PTSD seen in patients with delayed-onset PTSD (Liang et al., 1990). Whereas evidence suggests that biochemical correlates of moderate- and high-arousal events facilitate encoding, it may be that extreme arousal may actually disrupt encoding, with the result that memory for some traumatic events becomes fragmented (Koss, Tromp, & Tharan, 1995).

An important recent human investigation addresses the relationship between catecholamine activation and acquisition of memory. Cahil, Prins, Weber, and McGaugh (1994) examined the effect of propranolol, a drug that blocks beta-adrenergic activation, on long-term memory for an emotionally arousing story in comparison with a closely matched emotionally neutral story among normal controls. In randomized double-blind fashion, participants received either propranolol or a placebo 1 hour before viewing a series of slides. Some of the slides depicted scenes that were considered to be neutral in nature (e.g., one of the neutral slides showed a mother and her son walking together), whereas others depicted scenes that were classified as stressful and emotional (e.g., the boy in a terrible automobile accident). In a surprise memory test 1 week after viewing the slides, participants were tested for their memory of the slides. Participants in the placebo-condition group had significantly better memory for the emotional slides than for the neutral slides. Conversely, subjects in the propranolol-condition group did not remember the emotional slides any better than the neutral slides. That is, propranolol did not affect memory for the neutral slides but did affect memory for the emotionally arousing slides, suggesting that beta-adrenergic activation is involved in the enhanced memory associated with arousing or emotional experiences. The results could not be explained by potential effects of propranolol on attention or sedation.

Support for the idea that catecholamine stimulation also can facilitate memory retrieval for arousing or emotional experiences comes from a study of 20 Vietnam combat veterans with PTSD who, in response to disinhibition of the noradrenergic system by yohimbine infusion, experienced vivid intrusive memories of traumatic combat experiences. Forty percent had a full-blown flashback (Southwick et al., 1993). These intrusive recollections were accompanied by evidence of increased catecholamine activity, including significant elevations of MHPG, heart rate, and blood pressure. The retrieval of traumatic memories with yohimbine infusion is consistent with animal studies demonstrating enhanced retrieval of aversive memories through adrenergic and noradrenergic stimulation (Conway, Anderson, & Larsen, 1994). Creating a biological context (i.e., yohimbine-induced increase in catecholamine activity) that resembles the biological state at the time of encoding (fear-induced increase in catecholamine activity) may have served to facilitate the retrieval of frightening memories.

OTHER CONSIDERATIONS

Other models, such as learned helplessness (a maladaptive behavioral depression resulting from inescapable stress), have also been offered as ways to understand the development of PTSD (Krystal, 1990; Rasmusson & Charney, 1997). In all models of PTSD, the role of premorbid and developmental factors must be considered. To what degree are sensitization, fear conditioning, learned helplessness, and enhanced memory for trauma affected by neurobiological factors that have been inherited or influenced by the course of development?

Clearly, heredity plays a key role in animal and human behavior, including defensive and fear-related behaviors (LeDoux, 1996). For example, it is well known that animals can be bred for a variety of behavioral traits, including responsivity (ranging from timid to courageous) to novel stimuli. In general, these traits remain relatively stable over time (Gray, 1987). Similarly, in humans, it is believed that temperament and the individual's characteristic response to stressful stimuli are, in part, genetically determined (Kagan & Snidman, 1991; Marks, 1987). It is possible that these inherited behavioral traits and their neurobiological underpinnings influence the chances of developing PTSD when confronted with a traumatic stressor. For example, inherited variations in sympathetic nervous system functioning, the capacity for a particular neurobiological system to become sensitized or conditioned, or both may be, in part, genetically determined. Empirical evidence for a heritable component of PTSD comes from family history data supporting a relationship between PTSD and other anxiety disorders (J. Davidson, Smith, & Kudler, 1989) and from twin-study data suggesting that approximately 13% to 34% of the variance for specific PTSD-symptom clusters is genetically transmitted (True et al., 1993).

Experiences during early development also have an important influence on later behavioral and neurobiological responses to stress. It has been proposed that trauma in childhood may differentially affect maturation of various brain regions by overstimulating areas involved in fear and alarm reactions (limbic, midbrain, and brain stem) and by retarding cortical development through neglect and sensory deprivation (Perry, Pollard, Blakely, Baker, & Vigilante, 1995). Development and responsivity of various stress-related neuroendocrine systems might also be affected. Such effects would likely influence a child's ability to regulate impulses, aggression, and emotions and to accurately process information. It also is possible that early trauma-related neurobiological alterations might predispose an individual to develop PTSD in the future (Pynoos, Steinberg, & Wraith, 1995). For example, combat veterans with histories of childhood abuse are more likely to develop combat-related PTSD than are soldiers without histories of abuse (Bremner, Southwick, Johnson, Yehuda, & Charney, 1993).

Animal studies have provided strong support for the notion that severe psychological stress can cause tissue damage to the nervous system. Functional and morphological changes within the hippocampus have been reported in traumatized rodents and primates (Sapolsky, 1994). These changes may be mediated by stress-induced elevations of glucocorticoids. In humans, several recent magnetic resonance imaging (MRI) studies have reported decreased hippocampal volume in traumatized civilian and combat veteran populations with PTSD compared with controls (Bremner et al., 1995; Bremner, Randall, et al., 1997; Gurvits et al., 1996; Stein, Hanna, Koverola, Torchia, & McClarty, 1997). Because the hippocampus plays an important role in memory and learning, researchers investigated whether stress-induced damage to the hippocampus could help to explain reexperiencing symptoms, reported deficits in explicit memory, and fragmented memory for details of the traumatic event among subjects with PTSD.

In addition to MRI studies that raise the possibility of structural brain abnormalities (i.e., reduced hippocampal volume) among PTSD subjects, brain imaging studies with PET suggest that PTSD may also be associated with functional brain alterations. Preliminary PET studies indicate that when PTSD subjects are exposed to reminders of their personal trauma (e.g., traumatic images or scripts), they exhibit increased regional cerebral blood flow to brain structures thought to process emotionally charged information, such as the amygdala and the anterior cingulate cortex (Rauch & Shin, 1997). These findings appear to be consistent with the above models of PTSD.

In this brief review, we have touched on some of the most consistent neurobiological findings in humans with PTSD. We also have described a number of models that may help to explain these findings. Clearly, the neurobiology of acute and chronic trauma, as well as PTSD, is extremely complex. Human research in this area is still in its infancy.

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